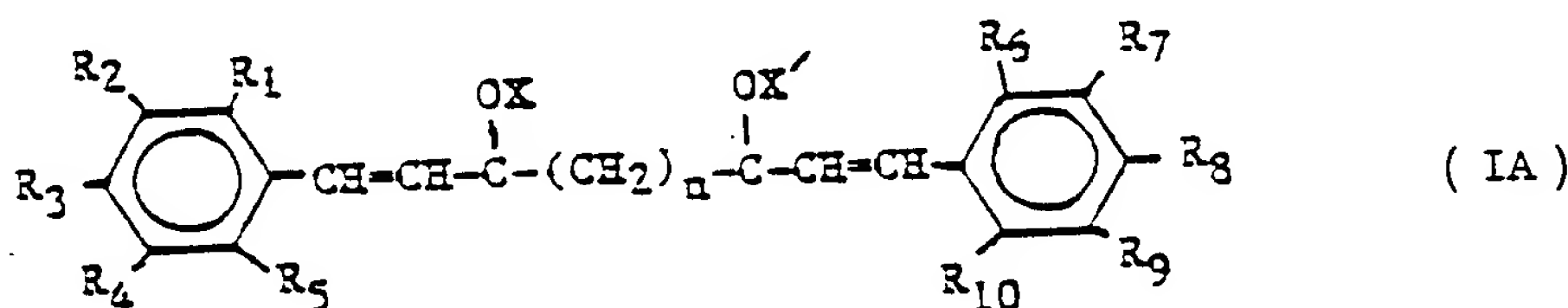




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/19, 31/075, 31/045 A61K 31/12	A1	(11) International Publication Number: WO 94/04139 (43) International Publication Date: 3 March 1994 (03.03.94)
(21) International Application Number: PCT/US93/07879 (22) International Filing Date: 23 August 1993 (23.08.93) (30) Priority data: 07/933,470 21 August 1992 (21.08.92) US (60) Parent Application or Grant (63) Related by Continuation US 933,470 (CIP) Filed on 21 August 1992 (21.08.92) (71) Applicants (for all designated States except US): DANA FARBER CANCER INSTITUTE [US/US]; 375 Longwood Avenue, Boston, MA 02115 (US). BETH ISRAEL HOSPITAL [US/US]; Dana Building - 909, 330 Brookline Avenue, Boston, MA 02115 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : PARDEE, Arthur, B. [US/US]; 30 Codman Road, Brookline, MA 02146 (US). LI, Jia-Qiang [— /US]; 1575 Tremont Street, Apt. 608, Boston, MA 02120 (US). CRUMPACKER, Clyde [— /US]; 65 Leonard Street, Gloucester, MA 01930 (US). ZHANG, Lin [— /US]; 14 Buswell Street, Boston, MA 02215 (US). (74) Agents: CONLIN, David, G. et al.; Dike, Bronstein, Roberts & Cushman, 130 Water Street, Boston, MA 02109 (US). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>

(54) Title: TREATMENT OF HUMAN VIRAL INFECTIONS**(57) Abstract**

Treatment of cells or humans carrying or infected with a virus capable of causing an immunodeficiency disease with particular compounds including those of formula (IA), wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group consisting of hydrogen and a chemical bond, and R₁ through R₁₀ are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

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TREATMENT OF HUMAN VIRAL INFECTIONSBACKGROUND OF THE INVENTION

The human immunodeficiency virus type 1 (HIV-1, also referred to as HTLV-III LAV or HTLV-III/LAV) and, to a lesser extent, human immunodeficiency virus type 2 (HIV-2) is the etiological agent of the acquired immune deficiency syndrome (AIDS) and related disorders. Barre-Sinoussi, et al., Science, 220:868-871 (1983); Gallo, et al., Science, 224:500-503 (1984); Levy, et al., Science, 225:840-842 (1984); Popovic, et al., Science, 224:497-500 (1984); Sarngadharan, et al., Science, 224:506-508 (1984); Siegal, et al., N. Engl. J. Med., 305:1439-1444 (1981); Clavel, F., AIDS, 1:135-140. This disease is characterized by a long asymptomatic period followed by the progressive degeneration of the immune system and the central nervous system. Studies of the virus indicate that replication is highly regulated, and both latent and lytic infection of the CD4 positive helper subset of T-lymphocytes occur in tissue culture. Zagury, et al., Science, 231:850-853 (1986). The expression of the virus in infected patients also appears to be regulated as the titer of infectious virus remains low throughout the course of the disease. Both HIV-1 and 2 share a similar structural and function genomic organization, having regulatory genes such as tat, rev, nef, in addition to structural genes such as env, gag and pol.

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While AIDS, itself, does not necessarily cause death, in many individuals the immune system is so severely depressed that various other diseases (secondary infections or unusual tumors) such as herpes, cytomegalovirus, Kaposi's sarcoma and

5 Epstein-Barr virus related lymphomas among others occur, which ultimately results in death. These secondary infections may be treated using other medications. However, such treatment can be adversely affected by the weakened immune system. Some humans infected with the AIDS virus seem to live many years with little

10 or no symptoms, but appear to have persistent infections. Another group of humans suffers mild immune system depression with various symptoms such as weight loss, malaise, fever and swollen lymph nodes. These syndromes have been called persistent generalized lymphadenopathy syndrome (PGL) and AIDS

15 related complex (ARC) and may or may not develop into AIDS. In all cases, those infected with the HIV are believed to be persistently infective to others.

The activation of the latent HIV provirus from the

20 asymptomatic period has been reported to be governed by a long terminal repeat (LTR) in the viral DNA. See, e.g. Ranki, A., et al., Lancet *ii*: 589-593 (1987); Fauci, A.S., et al., Science, 239:617-622 (1988); Zagury, D., et al., Science, 231:850-853 (1985); Mosca, J.D., Nature (London), 325:67-70 (1987). The

25 activity of HIV-1 is determined by the complex interaction of positive and negative transcriptional regulators that bind to specific sequences within the LTR. Cullen, B.R., et al., Cell, 58:423-426 (1989). Changes in the quantity or quality of these factors may underlie the activation of transcription of HIV-1

30 and HIV-2 latent provirus by a myriad of stimuli. See, e.g. Fauci, A.S., Science, 239:617-622 (1988); Griffin, G.E., et al., Nature (London), 339:70-73 (1989); Nabel, G., et al., Science, 239:1299-1302 (1988). Specifically, phorbol

35 12-myristate-13-acetate (PMA) and Tumor Necrosis Factor- α (TNF α) are believed to be potent activators. In particular,

-3-

NF α is present in markedly enhanced levels in HIV infected individuals, suggesting that the cytokine plays an important role in the pathogenesis of AIDS. Lahdevirta, J., Am. J. Med., 85:289-291 (1988).

5

Most known methods for treating individuals infected by HIV have focused on preventing integration of the provirus into the host cell's chromosome. Thus, one area of interest has been drugs that affect reverse transcriptase. Many of the proposed therapeutic methods, however, have not proven clinically effective. Indeed, even treatments that have resulted in clinical utility such as AZT (zidovudine) have not been reported to prevent the breakdown of the immune system in many patients after a number of years of treatment. Few methods have been reported to inhibit both expression of integrated provirus and chronic infection of HIV-1. Reverse transcriptase inhibitors e.g. AZT, ddC, ddI have not been reported to have inhibitory effect on chronic infections. Ro3-3335 was reported to be effective on chronic infection. See Hsu, M-C, Science, 254:1799-1800 (1992).

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It thus would be desirable to have a new compound that can treat HIV infected cells. It would be particularly desirable to have a new therapy that can be used to treat cells already infected, by means other than by preventing integration of the virus such as inhibitory expression of provirus, or keeping the provirus dormant within infected cells.

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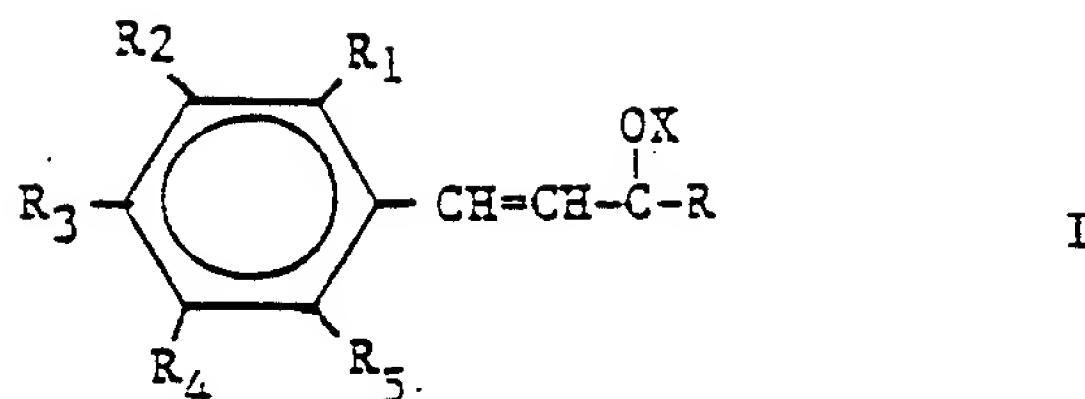
SUMMARY OF THE INVENTION

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We have now discovered that compounds of the following formula I are useful for treating cells infected by immunodeficiency viruses, preferably human immunodeficiency viruses such as HIV:

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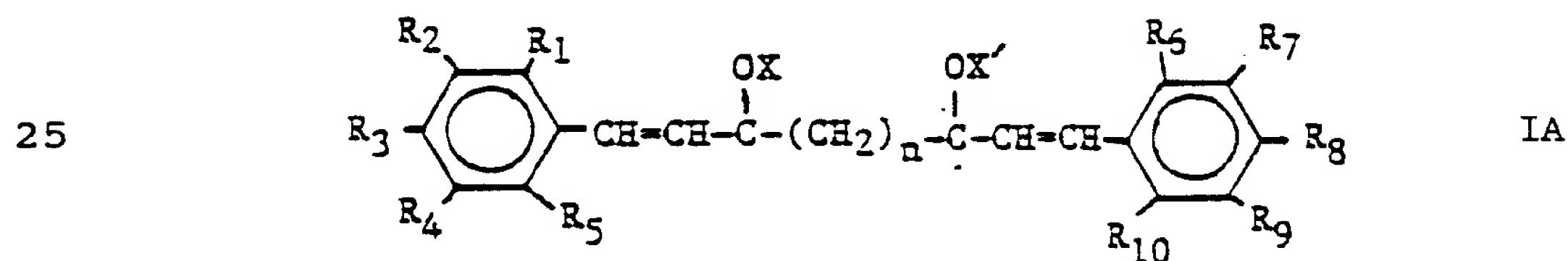
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wherein X is a bond or a hydrogen, R is selected from the group consisting of hydroxy and substituted alkylene, and R₁ through R₅ are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom such as N, O, S, and substituted and unsubstituted heteroalkyl. Preferably the carbon-carbon double bond of a compound of formula I has a trans configuration.

In preferred aspects, compounds of the following formula IA are used for purposes of the present invention including for use in treating cells infected by immunodeficiency viruses, preferably human immunodeficiency viruses such as HIV:



25

wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group of a bond or a hydrogen, R₁ through R₅ are the same as defined above in formula I, and R₆ through R₁₀ are each independently selected and defined as said R₁ through R₅. Preferably the value n is from 1 to 4, and more preferably n is one. A specifically preferred compound is curcumin. The present

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invention includes use of compounds of formula IA where one or both of the carbon-carbon double bonds are of a trans configuration as well as where one or both of the carbon-carbon double bonds are of a cis configuration. Compounds of formula
5 IA where both the above depicted double bonds are of a trans configuration are generally more preferred.

The compounds of the present invention can reduce or inhibit expression of genes operably linked to the LTR of an
10 immunodeficiency virus such as HIV.

In one embodiment, the compounds of the present invention can treat cells infected acutely and chronically by immunodeficiency viruses, for example, HIV, preferably HIV-1,
15 and thus can be used to treat humans infected by HIV. For example, treatment of those diagnosed as having AIDS as well as those having ARC, PGL and those not yet exhibiting such conditions.

20 These compounds can be used against a different target than the conventional drugs being used to treat humans infected by HIV, e.g., reverse transcriptase inhibitors such as zidovudine (AZT), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC). Using such drugs in combination with the present
25 compounds is anticipated to result in a synergistic result. Similarly, the present compounds should be effective in cells that are resistant to such compounds. For example, compounds of the present invention can be used to block HIV-1 LTR directed expression in AZT resistant cell lines.

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The invention also provides pharmaceutical compositions comprising a compound of formula I or IA and a suitable carrier therefor for use in the conditions referred to above.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the inhibitory effects of curcumin (varying concentrations) on TNF α and PMA induced HIV LTR directed gene expression.

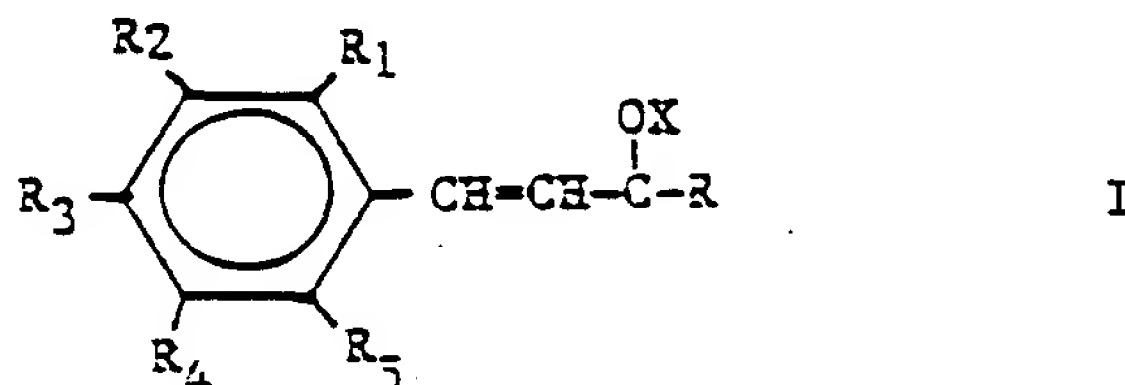
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Figure 2 shows the inhibition of HIV-1 replication by curcumin (varying concentrations) in acutely infected human peripheral blood mononuclear cells.

10 DETAILED DESCRIPTION OF THE INVENTION

We have discovered that compounds of the following formula I can be used to treat cells infected by an immunodeficiency virus, preferably human cells infected with HIV and thus can be used for treatment in HIV infected individuals:

15



20

wherein X is a chemical bond (i.e., forms a carbonyl group) or hydrogen, R is selected from the group consisting of hydroxy and a substituted alkylene group, e.g., an alkylene group having from 1 to about 15 carbon atoms, more preferably from about 1 to 8 carbon atoms, still more preferable from 1 to about 4 carbon atoms. The substituents of said alkylene group suitably may be, for example, halogen such as fluoro, chloro or bromo, alkyl such as alkyl having from 1 to about 12 carbon atoms or from 1 to 6 carbon atoms, alkenyl such as alkenyl having from 2 to 10 carbon atoms or 2 to 6 carbon atoms, alkynyl such as alkynyl having from 2 to about 10 carbon atoms or from 2 to 6 carbon atoms, aryl (including both substituted and unsubstituted aryl) having from 6 to 10 carbon atoms, and N, O, S, including heteroalkyl, e.g., heteroalkyl having one or more of said hetero atoms and

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from 1 to 10 carbon atoms or from 1 to 6 carbon atoms. Ring substituents R_1 , R_2 , R_3 , R_4 and R_5 are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom such as N, O, S, and substituted and unsubstituted heteroalkyl. Alkyl ring substituents suitably have from 1 to about 10 carbon atoms, more preferably 1 to 6 carbon atoms. Alkenyl and alkynyl phenyl ring substituents suitably have from 2 to about 10 carbon atoms, preferably 2 to 6 carbon atoms. Heteroalkyl ring substituents include groups containing one or more hetero atoms linkages and from 1 to about 15 carbon atoms, or from 1 to 8 carbon atoms. Preferred heteroalkyl ring substituents are alkoxy, aminoalkyl and thioalkyl groups where the specified heteroatoms is bonded to the aromatic ring and the substituents contain one or more carbon atoms, for example, 1 to about 10 carbon atoms, more preferably from 1 to about 4 carbon atoms. Said substituted R_1 through R_5 groups may be substituted at one or more available positions by one or more available groups such as, for example, alkyl groups such as alkyl groups having from 1 to 10 carbon atoms or from 1 to 6 carbon atoms, alkenyl groups such as alkenyl groups having from 2 to 10 carbon atoms or 2 to 6 carbon atoms, substituted and unsubstituted aryl groups having from 6 to 10 carbon atoms, halogen such as fluoro, chloro and bromo, and N, O and S, including heteroalkyl, e.g., heteroalkyl having from one or more of N, O and/or S linkages (and thus including alkoxy, aminoalkyl and thioalkyl) and from 1 to 10 carbon atoms or from 1 to 6 carbon atoms.

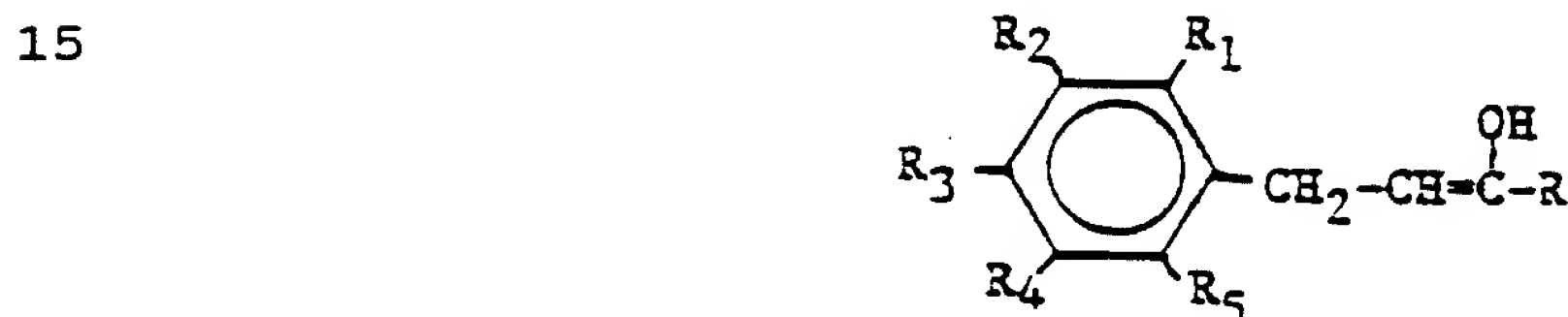
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Generally preferred are those compounds of formula I where the ring is at least mono-substituted, i.e., at least one of R_1 through R_5 is other than hydrogen. The phenyl ring suitably may be substituted by more than one group other than hydrogen, for example, di- or tri-substituted by groups other

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than hydrogen. Hydroxy and lower alkoxy such as methoxy and ethoxy are particularly preferred substituents on the phenyl ring.

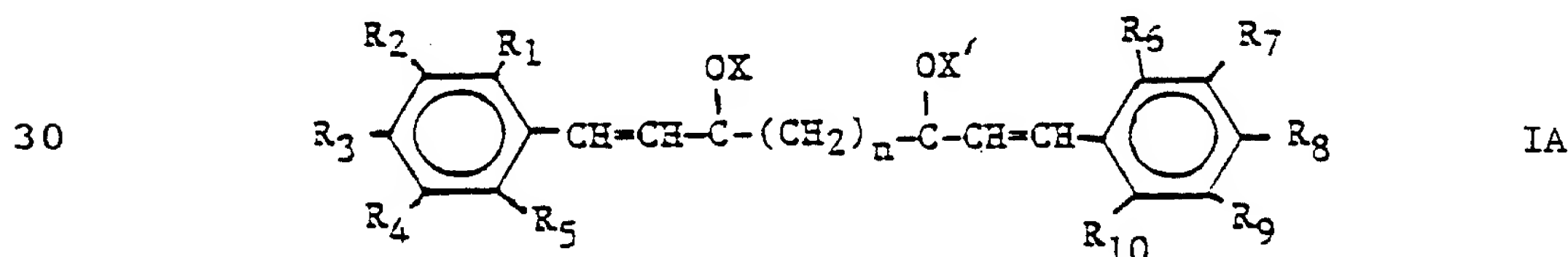
5 While compounds having the precise structure of formula I
where the double bond is conjugated with the phenyl ring are
preferred, as the terms are defined herein compounds coming
within formula I include structurally related compounds,
including those compounds where the depicted carbon-carbon
10 double bond is migrated to an adjacent carbon, e.g., the
compounds of the below structure where the group R and the ring
substituents R₁ through R₅ are the same as defined above for
formula I:



20

Such a structure may exist, e.g., where the substituent R stabilizes the depicted double bond such as by conjugation and/or intramolecular hydrogen bonding.

25 Generally more preferred for purposes of the present
invention are compounds of the following formula IA:



wherein the value n is an integer suitably from 1 to about 20, X
35 and X' are each independently selected from the group of a

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chemical bond (i.e., forms a carbonyl group) and a hydrogen,
R₁ through R₅ are the same as defined above in formula I,
R₆ through R₁₀ are each independently selected from the
group consisting of those groups set forth above to define R₁
5 through R₅ above, namely, hydrogen, hydroxy, halogen,
heteroatom of N, O, or S, substituted and unsubstituted alkyl,
substituted and unsubstituted alkenyl, substituted and
unsubstituted alkynyl, and substituted and unsubstituted
heteroalkyl.

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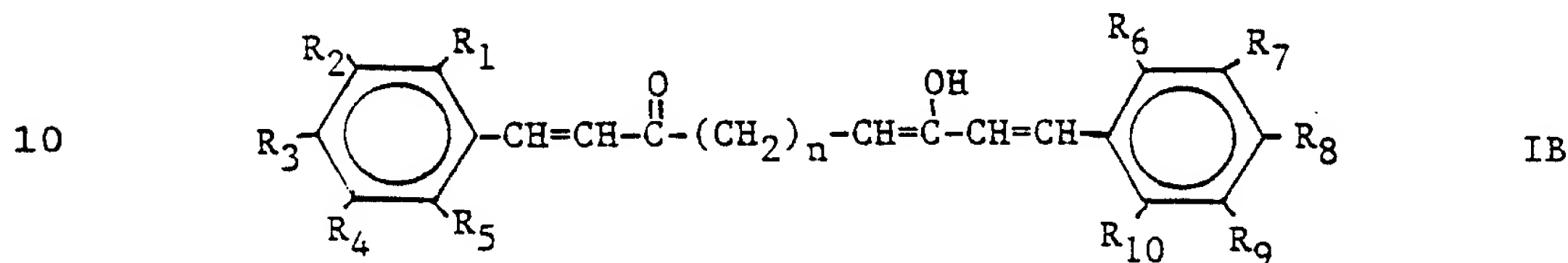
Preferably the value n of formula IA is a value of from 1
to 4, and more preferably n is one.

Generally preferred are those compounds of formula IA where
15 one or both of the phenyl rings are at least mono-substituted,
i.e. at least one of the substituents R₁ through R₁₀ is
other than hydrogen. Further preferred is where both of said
depicted rings are at least mono-substituted by a group other
than hydrogen. One or both of the phenyl rings may be
20 substituted by more than one group other than hydrogen, for
example, di- and tri-substituted by groups other than hydrogen.
Hydroxy and lower alkoxy such as methoxy and ethoxy are
particularly preferred ring substituents. More preferred is
where each of the above depicted phenyl rings has at least one
25 hydroxy group and at least one alkoxy group such as methoxy or
ethoxy. Meta and para ring positions are generally preferred
positions for substitution of a group other than hydrogen, and
more preferred is substitution of a hydroxy group at a para
position and an alkoxy group such as methoxy or ethoxy at a meta
30 position.

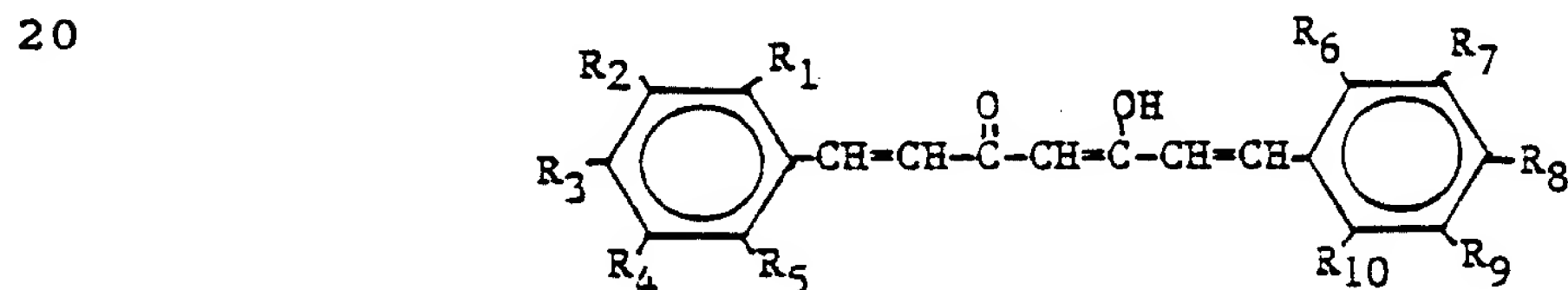
While compounds having the precise structure of formula IA
where the depicted carbon-carbon double bonds are conjugated
with the phenyl rings are preferred, as used herein, compounds
35 coming within formula IA include structurally related compounds,

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including those compounds where one or more of the depicted carbon-carbon double bonds or carbonyl groups is migrated to an adjacent carbon, e.g., compounds of the following formula IB where the ring substituents R_1 through R_{10} are the same as described above for formula IA and n is an integer of a value of zero or greater:



Such a structure will be more typical where stabilizing factors exist. For example, where the value n is zero, intramolecular hydrogen bonding and conjugation will stabilize the following compound where the ring substituents are as defined above:



25 In another embodiment, the invention includes use of related compounds such as bis(3,4-dihydroxy-cinnamoyl)methane and other diaryl compounds that comprise linkages between the two aryl groups such as alkanoyl, e.g., C_{1-10} -alkanoyl and specifically the group $(-CH_2C(O)(CH_2)_4-)$, and alkenoyl, e.g., C_{1-10} -alkenoyl and specifically the group $(-CH=C-C(O)(CH_2)_4-)$. The aryl groups of such diaryl compounds are suitably ring substituted with groups such as specified for substituents R_1 - R_{10} in reference to formula IA above.

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Compounds of the present invention can readily be made.
See, Merck Index, 417 (11th ed., 1989); T. Rao et al., Indian J. Med. Res., 75:574-578 (1982). Other compounds of formula I can be prepared by procedures well known to those skilled in the synthesis art.

One preferred compound, curcumin, has been used as a food additive for years. Curcumin was isolated in nineteenth century and has been identified as an active component of tumeric, the ground dried rhizome of the plant Curcuma Longa Linn. See, Ammon. H.P.T., et al., Pharmacology of Curcuma Longa, Planta Med., 57, 1-7 (1991). Satoskar, R.R., International Journal of Clinical Pharmacology, 24, 651-654 (1986); Flynn, D.L., Prostaglandins Leukotrienes and Medicine, 22:357-360 (1986); Mukhopadhyay, A., et al., Agents and Actions, 12 (4):508-515 (1982); Rao, T.S., et al., Indian J. Med. Res., 75:574-578 (1982); Sharma, O.P., Biochemical Pharmacology, 25:1811-1812 (1976); Koch, R.T., Eine Droge Zyr Gebrauch gegen Erkankungen der Gallenwege und der leber, Munch Med. Wschr., 972 (1927). Curcumin and certain related compounds have been reported to exhibit antiinflammatory activity. Thus, its use, and the use of related compounds is expected to pose little, if any, health risks and have at most extremely minor side effects.

It is believed that the compounds of the present invention provide effective therapy of chronically infected cells (i.e. cells infected by a virus which is an immunodeficiency virus such as FIV, SIV, HIV, etc.) as evidenced by a reduction in, preferably a complete repression of, e.g. HIV LTR directed gene expression. Thus, in an HIV infected cell addition of an effective amount of a compound of the present invention will reduce the expression of a gene operably linked to the HIV LTR. Preferably the gene is operably linked to an HIV-1 LTR. As used herein, the term operably linked means that the gene is under the control of the HIV LTR and positioned in a nucleotide

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sequence to accomplish this. Typically, the gene is downstream of the LTR, which acts as a promoter. Preferably, the gene corresponds to a viral gene such as the HIV env gene, HIV tat gene, HIV rev gene, etc.

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Hence, in one preferred embodiment the present invention can be used in treating those diagnosed as having AIDS as well as those having ARC, PGL and those seropositive but asymptomatic patients. For example, as a preventative, it can also be used prophylactically as a preventative for high risk individuals.

10

Compounds of the present invention can be used to treat cells, especially mammalian cells and in particular human cells, infected by an immunodeficiency virus such as HIV infected cells. As a result of treatment with compounds of the present invention viral expression is significantly reduced.

15

For example, HIV viral expression can be studied by a number of methods such as looking at the expression of a marker gene, e.g. CAT, LacZ, etc., operably linked to the HIV LTR, which acts as the promoter. Use of the present compounds such as curcumin can significantly reduce expression of such a marker. HIV viral expression is turned on and enhanced by HIV LTR stimulators such as tumor necrosis factors- α (TNF α) or phorbol 12-myristate-13-acetate (PMA). One product of this expression, i.e. tat can further augment such viral expression. Using a marker gene such as LacZ operably-linked to the HIV LTR in HIV infected cells, the addition of an effective amount of compounds of formula I significantly inhibits expression of lacZ gene product, thereby indicating that HIV expression under the control of the HIV LTR such as HIV envelope glycoprotein expression has been inhibited if not completely stopped.

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P²⁴, a major structural protein (product of gag), has been widely used for monitoring HIV-1 replication in cells and

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vireamia in individuals. Use of present compounds such as curcumin, at concentrations that do not adversely affect cells, can dramatically reduce HIV-1 replication, e.g. preferably a reduction of HIV-1 replication of more than 25% as determined by P²⁴ levels, more preferably a reduction of more than 50%, and still more preferably a reduction of HIV-1 replication of more than 80% as determined by P²⁴ levels.

The effective amount of a compound of the present invention used to obtain such a result can be at micromolar concentrations. Furthermore, the administration of the compounds of the present invention at effective concentrations, which inhibit HIV expression, has not been found to adversely affect treated cells.

The compounds of the present invention can be administered to HIV infected individuals or to individuals at high risk for HIV infection. For example, those having sexual relations with an HIV infected partner, intravenous drug users, etc. Because of its inhibitory effect, the compounds of the present invention and a pharmaceutical compositions comprising one or more compounds of formula I can be used prophylactically as a method of prevention for such individuals to minimize their risk. One would administer the compound at an effective amount as set forth below by methodology such as described herein.

As demonstrated in the examples which follow, compounds of the present invention block activation or suppress activity of HIV-1 LTR and HIV-1 expression in infected cells. In particular, it has been found that compounds of the present invention in a dose dependent fashion inhibit HIV LTR directed TNF α and PMA stimulated gene expression. Moreover, such inhibition is provided with essentially no adverse effects on cell survival or cellular mRNA or total cellular RNA synthesis. Thus, it is believed compounds of the present invention will

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have utility in inhibiting the progression of an HIV infection and other retroviral infections in cells and in a human, including utility in extending the latency of an HIV infection in humans.

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While not wishing to be bound by theory, the absence of cytotoxicity of the compounds of the present invention indicates that these compounds affect positive or negative regulators of LTR such as the HIV LTR, preferably HIV-1 LTR, that are more critical to the retrovirus than the host cell.

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Preferably, for inhibiting or reducing the expression of genes operably linked to an HIV LTR, one or more compounds of the invention is administered in an amount sufficient to reduce the amount of protein expressed by the gene by at least about 25 percent relative to an untreated cell, more preferably an amount sufficient to reduce the amount of protein by at least about 50 percent and still more preferably a reduction of the amount of protein expressed by at least about 75 percent relative to an untreated cell.

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In general for the treatment of immunodeficiency viral infections, for example an HIV infection, a preferred effective dose of one or more compounds of the present invention, in particular compounds of formula IA, will be in the range 0.1 mg to 5g per kilogram body weight of recipient per day, more preferably in the range of 0.1 mg to 1,000 mg per kilogram body weight per day, and still more preferably in the range of 1 to 600 mg per kilogram of body weight per day. The desired dose is suitably administered once or several more sub-doses administered at appropriate intervals throughout the day, or other appropriate schedule. These sub-doses may be administered as unit dosage forms, for example, containing 100 to 4,000 μ g, preferably 100 to 2,000 μ g.

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Preferably a compound of formula I or formula IA is used in accordance with the present invention in an isolated form distinct as it may be naturally found and in a comparatively pure form, e.g., at least 85% by weight pure, more preferably at least 95% pure. For some treatments in accordance with the present invention, it may be desirable that administered compound of formula I or IA at least 98% or even greater than 99% pure. Such a material would be considered sterile for pharmaceutical purposes. Potential contaminants include side products that may result upon synthesis of a compound of the invention or materials that may be otherwise associated with the compound prior to its isolation and purification. The present compounds should preferably be sterile and pyrogen free. Purification techniques known in the art may be employed, for example chromatography.

Administration of the compounds of the invention may be by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal) with oral or parenteral being preferred. It will be appreciated that the preferred route may vary with, for example, the condition and age of the recipient.

The administered ingredients may be used in therapy in conjunction with other medicaments such as reverse transcriptase inhibitors such as dideoxynucleosides, e.g. zidovudine (AZT), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC), TAT antagonists such as Ro 3-3335 and Ro 24-7429 protease inhibitors and other agents such as 9-(2-hydroxyethoxymethyl)guanine (acyclovir), interferon, e.g., alpha-interferon, interleukin II, and phosphonoformate (Foscarnet) or in conjunction with other immune modulation agents including bone marrow or lymphocyte transplants or other medications such as levamisole or thymosin which would increase lymphocyte numbers and/or function as is

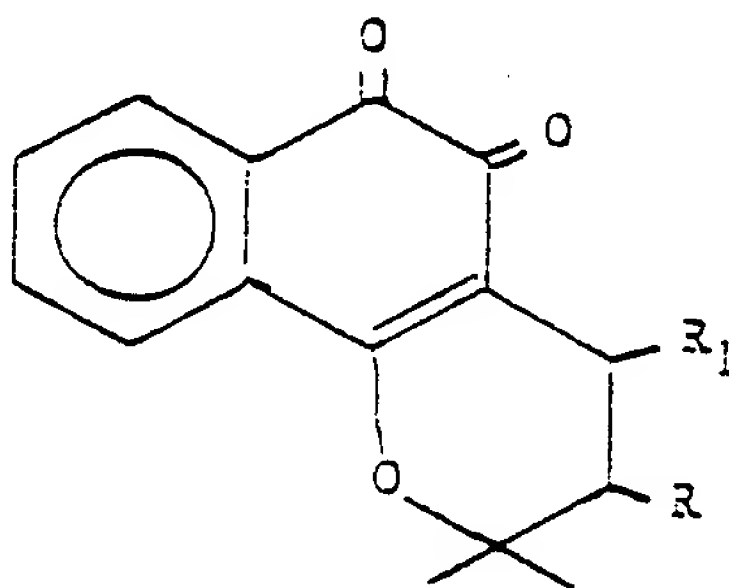
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appropriate. Because many of these drugs are directed to different targets, e.g., viral integration, it is anticipated that a synergistic result will be obtained by this combination.

5 Similarly, the present compounds may be effective when the above-described drugs are not or are no longer effective. For example, compounds of the present invention can be used in cells that are resistant to reverse transcriptase inhibitors such as AZT, ddI, and ddC. For instance, the compounds of formula (I),
10 can be used to block HIV-1 LTR directed LTR expression in such resistant cell lines and for treatment of such resistant strains. For example, the present compounds can block HIV-1 LTR directed expression in an AZT resistant strain of HIV-1. Accordingly, the present invention can be used therapeutically
15 in an individual as that individual develops resistance to drugs that act on different targets such as AZT, ddI, ddC, R03-3335, etc. It is expected that the present invention can be used for treatment of HIV-1 infected individuals who develop resistance to any drug that targets a different state in the viral life
20 cycle than the present compounds.

In one preferred embodiment one or more compounds of formulas I or IA are used in conjunction with a compound of the following formula II:

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II

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wherein R and R₁ are each independently selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and
35 unsubstituted aryl, and substituted and unsubstituted alkoxy,

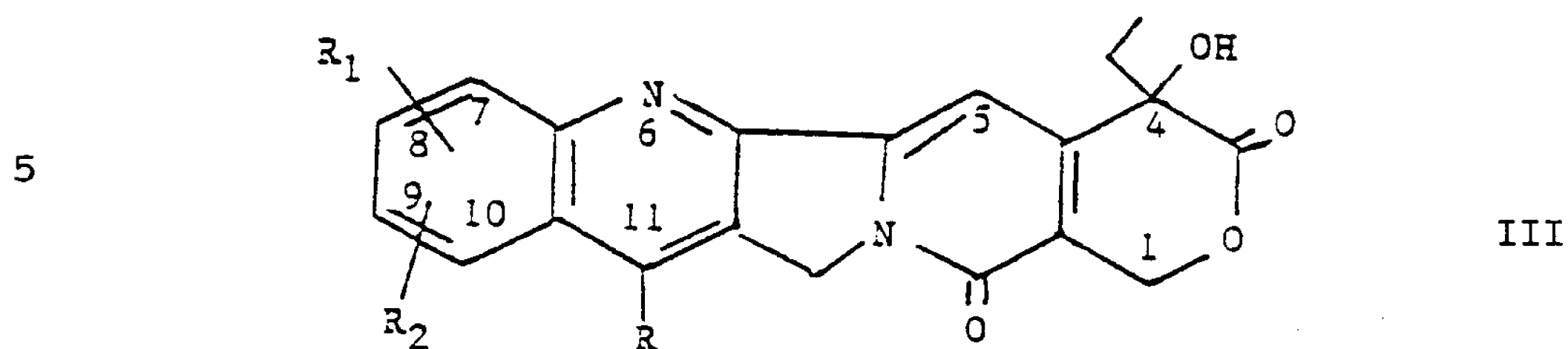
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with particularly preferred compounds of formula II including β -lapachone (i.e., R and R₁ both being hydrogen), and 3-allyl- β -lapachone (i.e., R being allyl and R₁ being hydrogen). The alkyl groups preferably have from 1 to about 15 carbon atoms, more preferably from 1 to about 10 carbon atoms, still more preferably from 1 to about 6 carbon atoms. The term alkyl as used in reference to formula II unless otherwise modified refers to both cyclic and noncyclic groups, although of course cyclic groups will comprise at least three carbon ring members. Straight or branched chain noncyclic alkyl groups are generally more preferred than cyclic groups. Straight chain alkyl groups are generally more preferred than branched. The alkenyl groups preferably have from 2 to about 15 carbon atoms, more preferably from 2 to about 10 carbon atoms, still more preferably from 2 to about 6 carbon atoms. Especially preferred alkenyl groups have 3 carbon atoms (i.e., 1-propenyl or 2-propenyl), with the allyl moiety being particularly preferred. Phenyl and naphthyl are generally preferred aryl groups. Alkoxy groups include those alkoxy groups having one or more oxygen linkage and preferably have from 1 to 15 carbon atoms, more preferably from 1 to about 6 carbon atoms. Said substituted R and R₁ groups may be substituted at one or more available positions by one or more suitable groups such as, for example, alkyl groups such as alkyl groups having from 1 to 10 carbon atoms or from 1 to 6 carbon atoms, alkenyl groups such as alkenyl groups having from 2 to 10 carbon atoms or 2 to 6 carbon atoms, aryl groups having from six to ten carbon atoms, halogen such as fluoro, chloro and bromo, and N, O and S, including heteroalkyl, e.g., heteroalkyl having one or more of said hetero atom linkages (and thus including alkoxy, aminolakyl and thioalkyl) and from 1 to 10 carbon atoms or from 1 to 6 carbon atoms.

Also preferred is to use one or more compounds of formula I or IA, either alone or in combination with a compound of formula

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II such as β -lapachone, in conjunction with a compound of the following formula III:



10 wherein R, R₁ and R₂ are each independently selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, noncyclic heteroalkyl, and substituted and unsubstituted alkenyl, provided at least two of the substituents of R, R₁ and R₂ are other than hydrogen; with particularly preferred
 15 compounds of formula III including Topotecan (i.e., the compound of formula III where R is hydrogen, R₁ is 9-hydroxyl, and R₂ is 10-N,N-dimethyl(methylene)amino (i.e., (CH₃)₂NCH₂-), and the compound of formula III where R is ethyl, R₁ is hydrogen and R₂ is 9-hydroxyl, wherein said 9- and 10-
 20 prefixes refer to positions of ring members as indicated in formula III above.

The alkyl groups preferably have from 1 to about 12 carbon atoms, more preferably from about 1 to 6 carbon atoms. The term
 25 alkyl as used in reference to formula III unless otherwise modified refers to both cyclic and noncyclic groups, although of course cyclic groups will comprise at least three carbon ring members. Straight or branched chain noncyclic groups are generally more preferred than cyclic groups. Straight chain
 30 alkyl groups are generally more preferred than branched. The alkenyl substituents preferably have from 2 to about 12 carbon atoms, more preferably from 2 to about 6 carbon atoms. Heteroalkyl groups include those noncyclic groups that comprise one or more hetero atoms and each hetero atom has one or more
 35 alkyl linkages such as alkyl linkages having from 1 to 8 carbon

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atoms or 1 to 4 carbon atoms. Thus suitable heteroalkyl groups include those where a hetero atom is directly bonded to the general ring system of formula I as well as those groups where a hetero atom is spaced from the ring system by an alkylene linkage of, e.g., one to four carbon atoms. Particularly preferred heteroalkyl groups include aminoalkyl groups including primary, secondary and tertiary alkylamines, and especially preferred are N-N-dialkyl(alkylene)amino groups, e.g., groups of the formula $(\text{alkyl})_2\text{N}(\text{CH}_2)_n$ where n is an integer of 1 to 4. A particularly preferred group is N-N-dimethylmethyleamino. The term "noncyclic" heteroalkyl, is intended to include straight and branched chain moieties, but not groups that comprise a closed ring structure including those groups that form a ring comprising two or more aromatic carbons at positions 7 to 10 as depicted above in formula III.

Said substituted R, R_1 and R_2 groups may be substituted at one or more available position by one or more suitable groups such as, for example, halogen such as fluoro, chloro or bromo, alkyl such as alkyl having from 1 to 12 carbon atoms or from 1 to 6 carbon atoms, alkenyl such as alkenyl having from 2 to 10 carbon atoms or 2 to 6 carbon atoms, aryl having from 6 to 10 carbon atoms, and N, O, S, including heteroalkyl, e.g., heteroalkyl alkyl having one or more of said hetero atoms and from 1 to 10 carbon atoms or from 1 to 6 carbon atoms.

The present invention includes use of both racemic mixtures and optically active stereoisomers of compounds of formula III. Typically preferred are optically active compounds where the chiral carbon of the lactone moiety (i.e., the ring carbon of position 4 as depicted in formula III above) is of the (R) configuration according to the Cahn-Ingold-Prelog nomenclature system. See Carey, F.A., Advanced Organic Chemistry, Part A, p. 65-66 (2d ed., Plenum Press 1984).

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Such compositions of compounds of formula I or IA used in combination with one or more compounds of formula II and/or III may be employed alone or in combination with acceptable carriers such as those described below. For the treatment of

5 immunodeficiency viral infections, for example an HIV infection, suitable effective dose of a compound of formula II in such a composition will be in the range of 1 to 5,000 μg per kilogram body weight of recipient per day, preferably in the range of 10 to 4,000 μg per kilogram body weight of

10 recipient per day; and a suitable effective dose of a compound of formula III in such a composition will be in the range of 0.4 to 10,000 μg per kilogram body weight of recipient per day, preferably in the range of 5 to 500 μg per kilogram body weight of recipient per day. When the compounds are

15 administered together it is expected one can use the lower portion of these ranges with excellent results.

One or more compounds of formula I or formula IA may be administered alone, or as part of a pharmaceutical composition,

20 comprising at least one compound of formula I or IA together with one or more acceptable carriers thereof and optionally other therapeutic ingredients, including those therapeutic agents discussed supra such as one or more compounds of formula II or III. The carrier(s) must be "acceptable" in the sense of

25 being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or

30 parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy.

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Such methods include the step of bringing into association the to be administered ingredients with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing
5 into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral
10 administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil
15 liquid emulsion, or packed in liposomes and as a bolus, etc.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active
20 ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid
25 diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Compositions suitable for topical administration include
30 lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier.

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Compositions suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising one or more compounds of the present invention and a pharmaceutically acceptable carrier. A suitable topical
5 delivery system is a transdermal patch containing the ingredient to be administered.

Compositions suitable for rectal administration may be presented as a suppository with a suitable base comprising, for
10 example, cocoa butter or a salicylate.

Compositions suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size, for example, in the range 20 to 500 microns which is
15 administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or
20 oily solutions of the active ingredient.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active
25 ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may
30 contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose
35 containers, for example, sealed ampules and vials, and may be

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stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile
5 powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard
10 to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

All documents mentioned herein are incorporated herein by reference.

15

The present invention is further illustrated by the following examples. These examples are provided to aid in the understanding of the invention and are not to be construed as limitations thereof.

20

GENERAL COMMENTS

The following reagents and procedures were employed as specified in the examples.

25

Virus. HIV-1 was obtained from the culture supernatant of HTLV-III_B-producing H9 (H9/HTLV-III_B) cells. During the exponential phase of growth, cell free supernatant was harvested, standardized for reverse transcriptase (RT) activity,
30 and frozen in aliquots at -70°C. Clinical isolates of HIV-1 were prepared from patients testing positive for the human immunodeficiency virus, and standardized for RT activity.

Cells. Cell clone 293.27.2 (23), obtained from L.A. Herzenberg (Stanford University), was derived from human
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embryonic kidney epithelial cells, which were cultured in Dulbecco's modified Eagle's medium (GIBCO) supplemented with 10% Fetal Calf Serum (FCS, obtained from Sigma) plus L-glutamine. See, e.g. Roederer, M., et al., Proc. Natl. Acad. Sci. USA,
5 87:4884-4888 (1990). This cell clone had been stably transfected with PNAZ, which is an expression construct of lacZ gene driven by HIV-1 LTR. Expression of β -galactosidase can be greatly induced by PMA or $\text{TNF}\alpha$. Human peripheral blood mononuclear cells (PBMC) were prepared by Ficoll-Hypaque
10 gradient centrifugation of blood from HIV-seronegative individuals, and cultured in RPMI 1640 supplemented with 20% FCS (Sigma), penicillin, streptomycin, and L-glutamine in the presence of PHA (3 $\mu\text{g}/\text{ml}$). RPMI 8402 cell line, a present from Toshiwo Ando (Aichi Cancer Research Institute, Nagoya,
15 Japan), is a human T lymphatic cell line. It was grown in RPMI 1640 medium supplemented with 15% FCS and L-glutamine.

Stock Solution. A stock solution of curcumin was prepared in ethanol at a 10 mM concentration. Aliquots of the stock
20 solution were stored frozen at -20°C .

Quantitation of HIV-1 LTR directed gene expression.
Exponentially growing 293.27.2 (L.A. Herzenberg of Stanford University) cells were plated in 6 well plates at 2×10^5
25 cells per well in 2 ml of growth medium. After 48 hours, cells were stimulated with 40 u/ml of $\text{TNF}\alpha$ (Genzyme, Cambridge, MA) or 2 ng/ml of PMA (Sigma). Various concentrations of the specified compound were added to the medium at designated times after stimulation with final concentrations of ethanol at less
30 than 0.1% (vol/vol). After 6-8 hours incubation at 37°C , medium was aspirated, cells were harvested, washed harvested, washed 4 times with PBS, and lysed in lacZ buffer (60 mM Na_2HPO_4 , 40 mM NaH_2PO_4 , 10 mM KCl, 1 mM MgSO_4). β -Galactosidase activities of cell lysates were quantitated
35 by using ONPG as substrate. See, e.g. Herbomel, et al., Cell,

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39:653-662 (1984). Protein concentration was measured. Cell viability was determined by the colony formation assay after cells were treated as above.

Treatment in acute HIV-1 infection. PBMC, after 72 hours stimulation with 3 μ g/ml PHA, were infected with either HTLV-III_B or a clinical isolate of HIV-1 at 1 reverse transcriptase unit (RTU) per 10 cells. Infection was carried out at 37°C for 2 hours. Then PBMC were washed with PBS to remove free virus and replated at 4.5×10^6 cells per well in 2 ml medium in the absence or presence of different concentrations of drugs. The cells were then continuously exposed to drugs for 6 days. On day 3, 1 ml of medium was removed from each well and replaced with 1 ml of fresh media containing drug at the previous concentration. On day 6, cells and media were harvested. Cell viability was determined by the trypan blue exclusion method and MTT metabolic assays. See, e.g. Mosman, T., J. Immunological Methods, 65:55-63 (1983). P²⁴ levels in the culture supernatant were quantitated by ELISA assay with HIV-1 P²⁴ Antigen Kinetics Assay Kit (Coulter, Hialeah, FL). RNA of HIV-1 reverse transcriptase was assayed with HIV-1 RNA Detection Kit (GeneTrak, Framingham, MA) according to manufacturer's instructions. Briefly, total cellular RNA was prepared, dot blotted onto a nitrocellulose membrane, and hybridized with ³²P labeled probe for RT RNA.

EXAMPLE 1

293.27.2 cells were plated in 6 well plates at 2×10^5 cells/well in 2 ml of growth medium (DMEM). TNF α (40 u/ml) and PMA (2 ng/ml) together with various concentrations of curcumin as indicated in Figure 1 were added to culture media 48 hours after the cells were plated. Six hours after addition of the curcumin, cells were harvested and β -galactosidase activity was measured with ONPG as the substrate with results

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depicted in Figure 1. Enzymatic activity is expressed as percentage of maximum expression which is referred to that in drug untreated sample (taken as 100).

5 EXAMPLE 2

Human PBMC were infected with HIV-1 (HTLV-III_B) at 37°C for 2 hours. Free virus were removed by wash with PBS. Infected PBMC were then aliquot into cells at 4.5 X 10⁵ cells/well. Various concentrations of curcumin as indicated in Figure 2 were added to culture media. After 6 days, cell viability was determined by trypan blue exclusion, P²⁴ levels were determined as described in the General Comments above. The results shown in Figure 2 are representative of two independent studies for which each data point was obtained from duplicate samples.

EXAMPLE 3

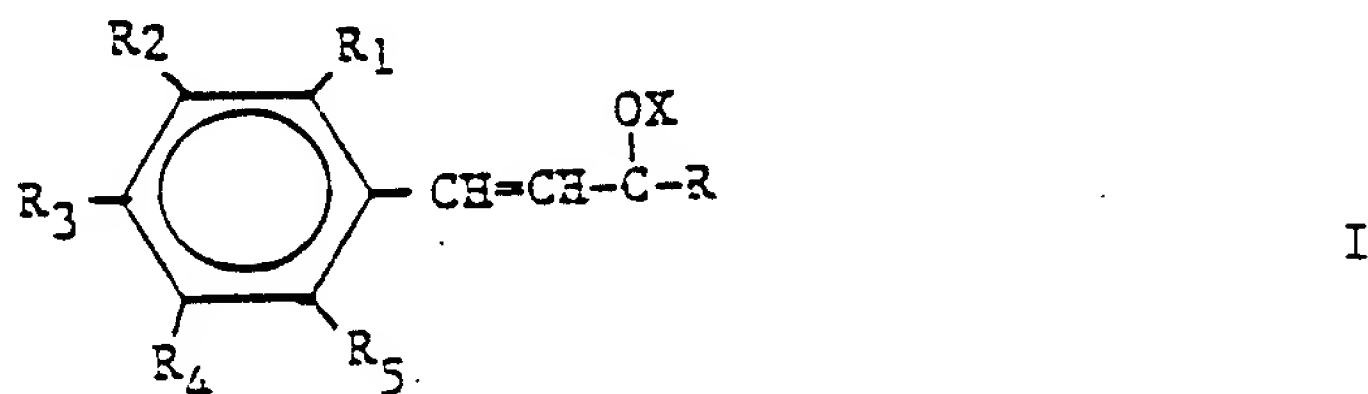
20 In a chronically infected T-lymphocyte and the promyelocytic cell line OM10.1, inhibition of P²⁴ antigen was seen at IC₅₀ - 4.58 μM following treatment with curcumin whereas AZT and ddI had little effect. The cell line OM10.1 contains one copy of HIV-1 per cell integrated into its genome and continually produces a low of HIV-1 proteins. This cell line was kindly supplied by NIH-AIDS Research and Reference Reagent Program.

30 This invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the disclosure, may make modification and improvements with the spirit and scope of the invention.

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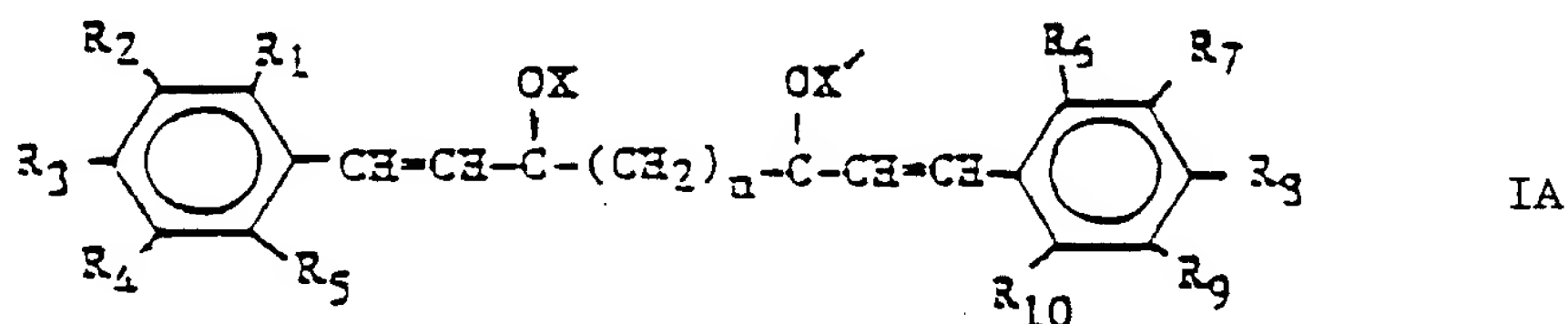
What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutical acceptable carrier and an effective antiviral treatment amount of a compound of the formula I:



X is selected from the group consisting of hydrogen and a chemical bond, R is selected from the group consisting of hydroxy and substituted alkylene, and R₁ through R₅ are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl, adapted for treating a mammal having an immunodeficiency virus.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective treatment amount of compound of the formula IA:

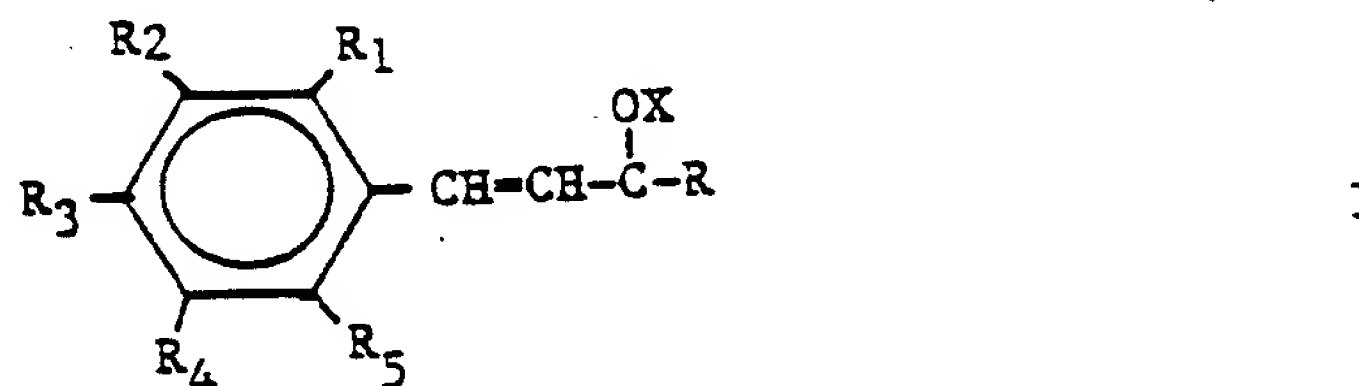


wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group consisting of

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hydrogen and a chemical bond, R_1 through R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl, adapted for treating a mammal having an immunodeficiency virus.

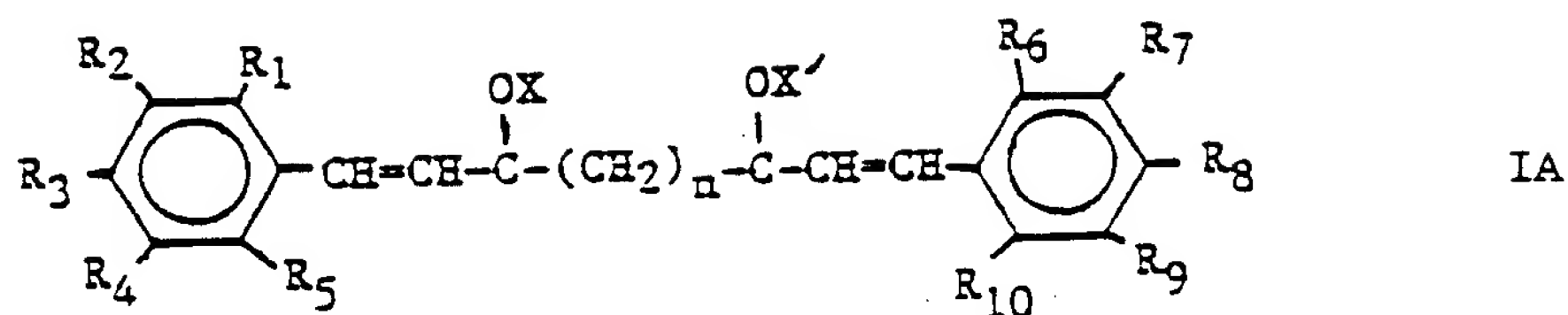
3. A method of inhibiting or reducing the expression of genes operably linked to a LTR of an immunodeficiency virus which comprises administering an effective gene expression reduction amount of a compound of the formula I:



X is selected from the group consisting of hydrogen and a chemical bond, R is selected from the group consisting of hydroxy and substituted alkylene, and R_1 through R_5 are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

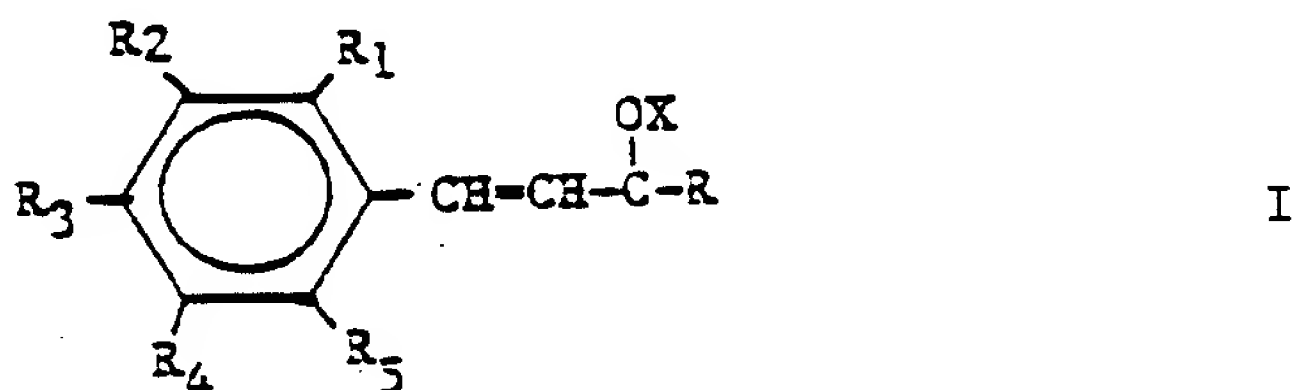
4. A method of inhibiting or reducing the expression of genes operably linked to an LTR of an immunodeficiency virus which comprises administering an effective gene expression reduction amount of a compound of the formula IA:

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wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group consisting of hydrogen and a chemical bond, R_1 through R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

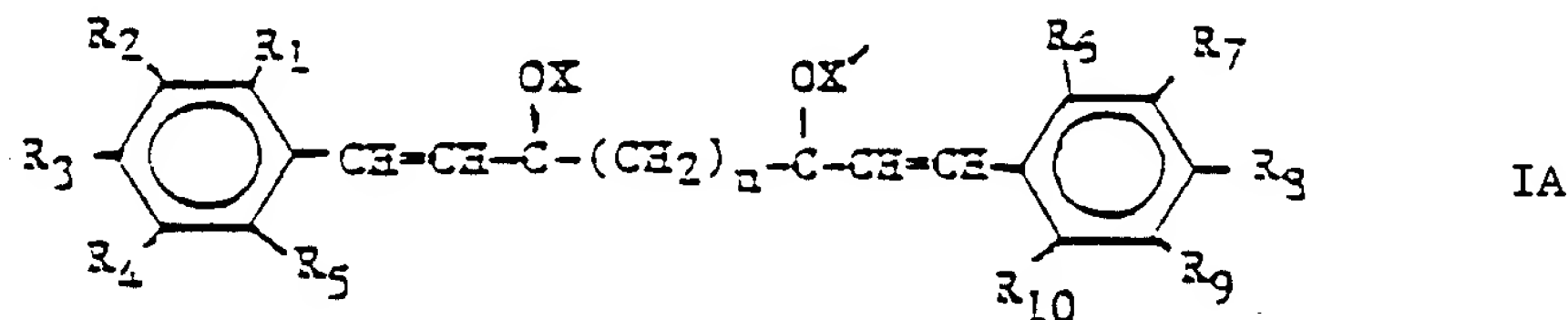
5. A method for treating cells infected with a virus capable of causing an immunodeficiency disease in a human, comprising administering to the cells an effective antiviral treatment amount of a compound of the following formula I:



X is selected from the group consisting of hydrogen and a chemical bond, R is selected from the group consisting of hydroxy and substituted alkylene, and R_1 through R_5 are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

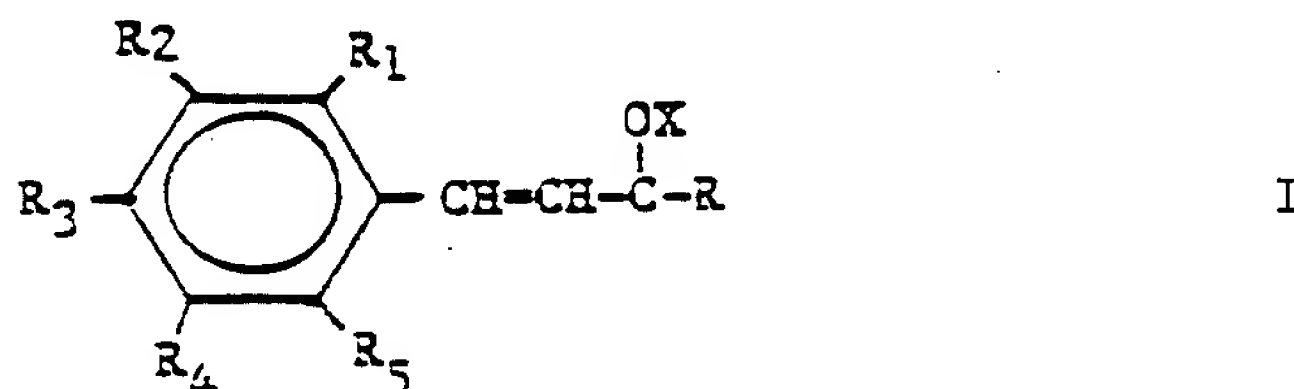
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6. A method for treating cells infected with a virus capable of causing an immunodeficiency disease in a human, comprising administering to the cells an effective antiviral treatment amount of a compound of the following formula IA:



wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group consisting of a chemical bond and hydrogen, and R_1 through R_{10} are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

7. A method of treating a human having an immunodeficiency disease comprising administering to said human an effective immunodeficiency disease treatment amount of a compound of the following formula I:

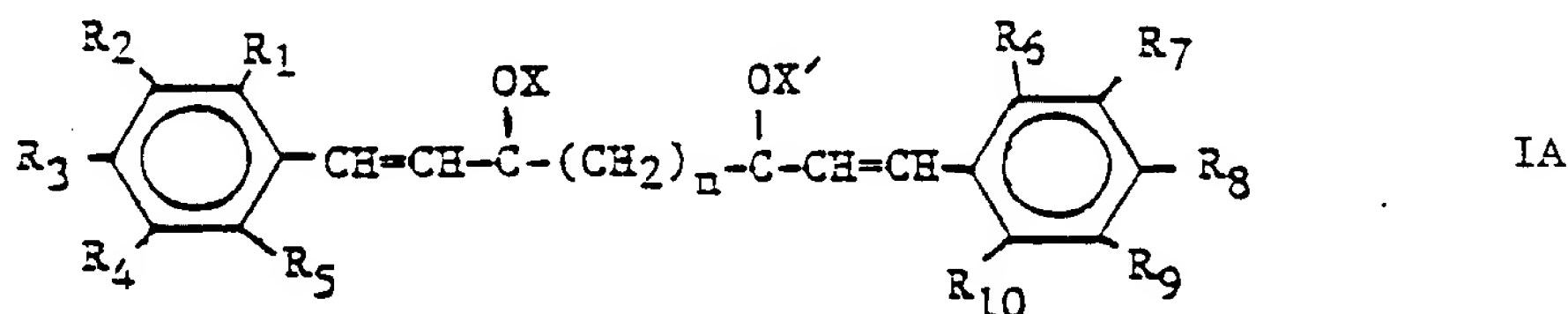


X is selected from the group consisting of a chemical bond and hydrogen, R is selected from the group consisting of hydroxy and substituted alkylene, and R_1 through R_5 are each independently selected from the group consisting of hydrogen,

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hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

8. A method of treating a human having an immunodeficiency disease comprising administering to said human an effective immunodeficiency disease treatment amount of a compound of the following formula IA:



wherein the value n is an integer from 1 to 20, X and X' are each independently selected from the group consisting of a chemical bond and hydrogen, and R₁ through R₁₀ are each independently selected from the group consisting of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, a heteroatom, and substituted and unsubstituted heteroalkyl.

9. The immunodeficiency virus of claims 1, 2, 3, 4, 5, 6, 7 or 8, which is resistant to a reverse transcriptase inhibitor.

10. The reverse transcriptase inhibitor described in claim 9, which is selected from the group consisting of zidovudine (AZT), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxycytidine (ddC).

11. The reverse transcriptase inhibitor described in claim 10 which is AZT.

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12. The method of claims 3 or 4 wherein the LTR is an HIV LTR.

13. The compound described in claims 2, 4, 6 or 8 where n is a value of from 1 to 4.

14. The compound described in claim 1, 2, 3, 4, 5, 6, 7 or 8 where the compound of formula I or IA is curcumin.

15. The method of claim 5 or 6 where the cells are mammalian cells.

16. The method of claims 5 or 6 where the cells are human cells.

17. The method of claims 5 or 6 where the virus is capable of causing in the human acquired immune deficiency syndrome or an acquired immune deficiency syndrome related complex.

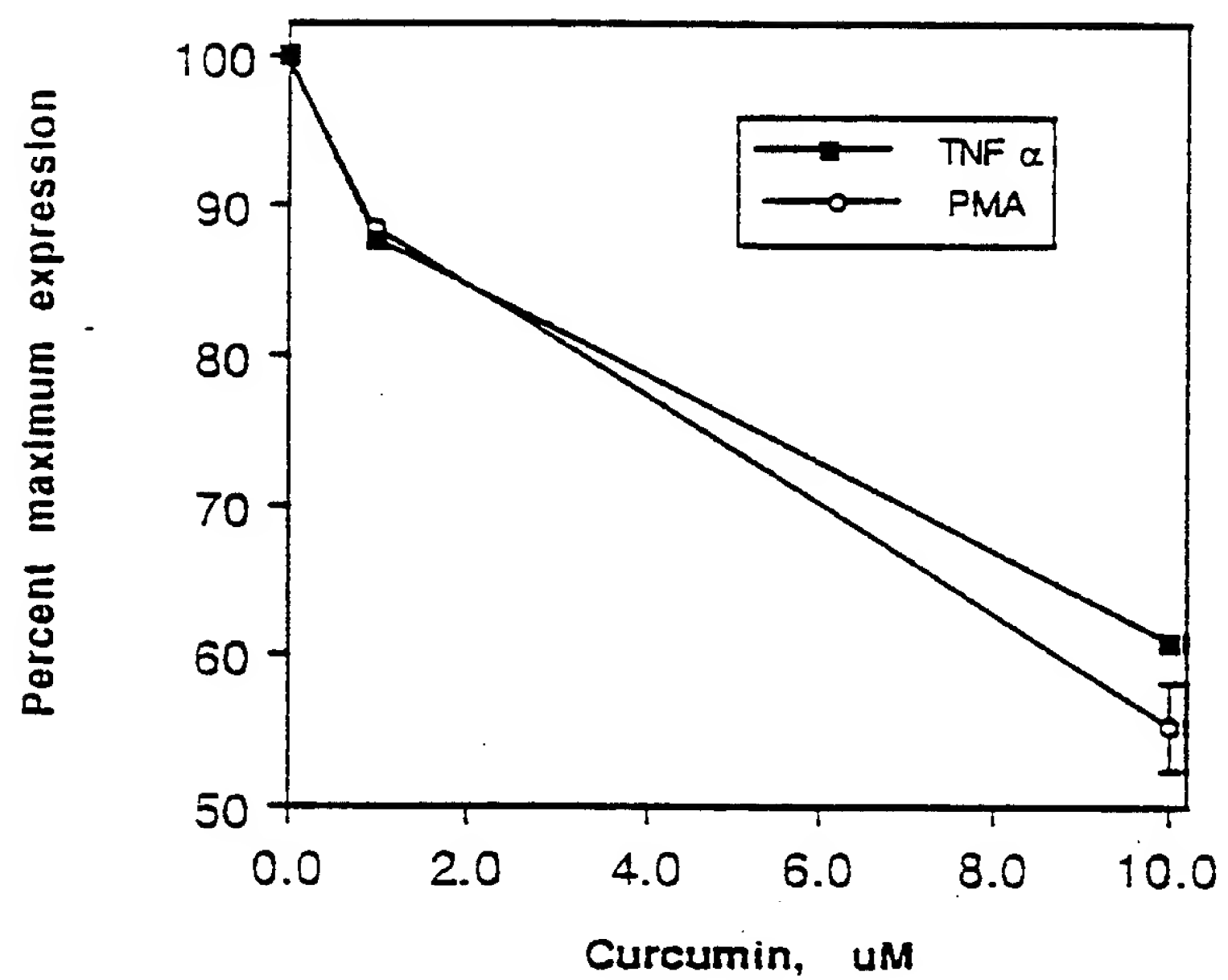
18. The method of claims 5 or 6 where the virus is HIV.

19. The method of claim 5 or 6 where the virus is HIV-1.

20. The method of claims 7 or 8 where the immunodeficiency disease is acquired immune deficiency syndrome or an acquired immune deficiency syndrome related complex.

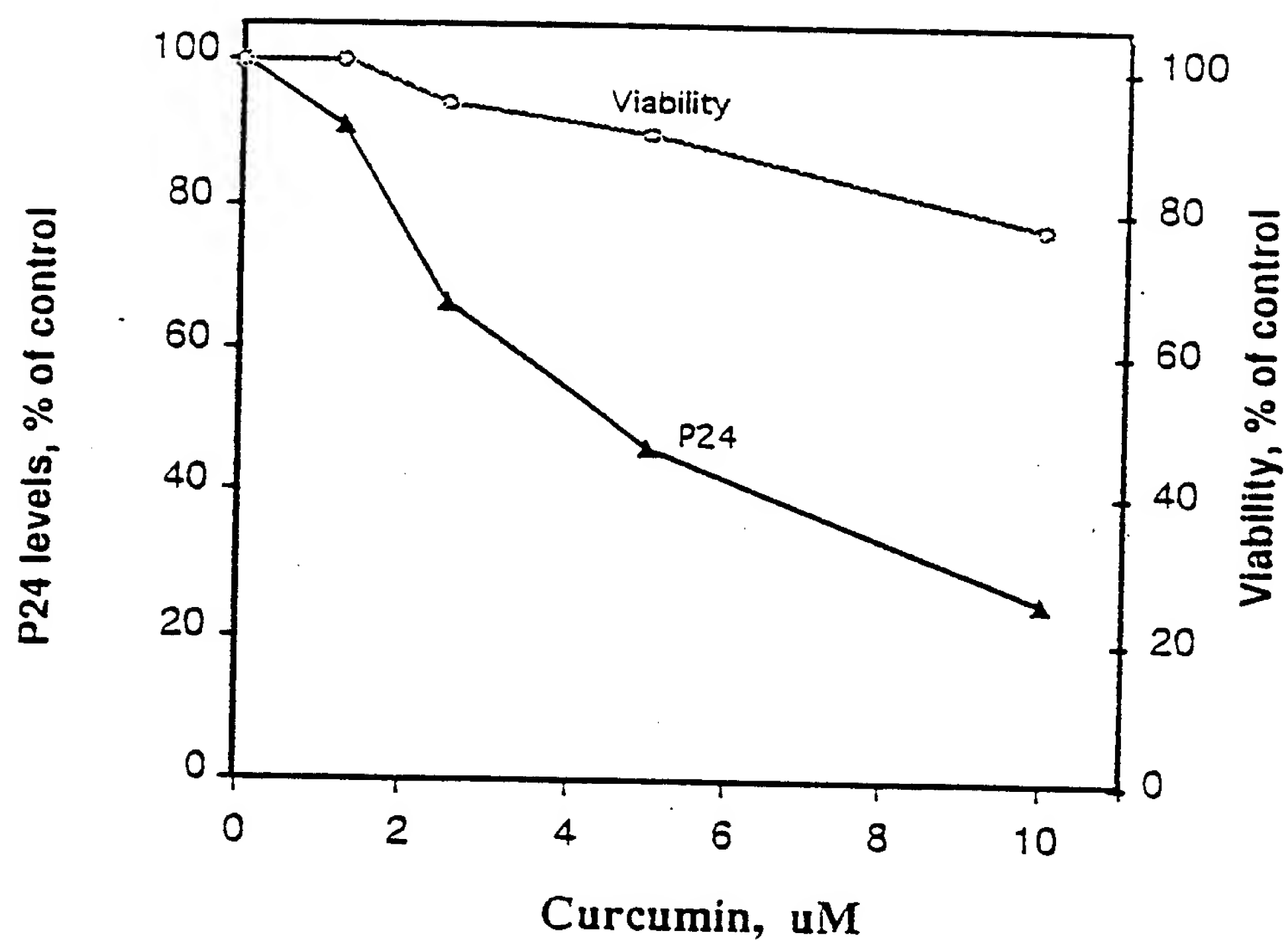
21. The method of claims 7 or 8 in which the human has antibodies to the HIV virus.

FIGURE 1



Inhibition by Curcumin on HIV LTR
directed cytokine induced gene expression

FIGURE 2



Inhibition of HIV-1 replication by Curcumin in acutely infected human peripheral blood mononuclear cells

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/07879

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/19, 31/075, 31/045, 31/12

US CL : 514/568, 678, 679, 717, 720, 726, 730

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/568, 678, 679, 717, 720, 726, 730

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN- compounds, Antiviral, AntiHIV, AIDS

APS-compound, Antiviral, Anti HIV, AIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, volume 114, no. 5, issued 04 February 1991, Sakagami et al, "Anti-influenza virus activity of synthetically, polymerized phenylpropenoids"., (Sch. Med., Showa Univ., Tokyo, Japan 142). Biochem. Biophys. Res. Commun. 1990, vol. 172, no. 3, pp. 1267-72 see the abstract no. 35491k.	1-21
Y	Chemical Abstracts, volume 110, no. 23, issued 05 June 1989, Bankova et al. "On the chemical composition of some propolis fractions with antiviral action"., (Inst. Microbiol., Bulg.). Acta Microbiol. Bulg. 1988, vol. 23, pp. 52-57, see the abstract no. 209208h.	1-21

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 18 NOVEMBER 1993	Date of mailing of the international search report 08 DEC 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer RUSSELL TRAVERS Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/07879

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, volume 110, no. 17, issued 24 April 1989, Take et al. "Comparative studies of the inhibitory properties of antibiotics on human immunodeficiency virus and avian myeloblastosis virus reverse transcriptases and cellular DNA polymerases"., (Sch. Med., Hiroshima, Univ., Hiroshima, Japan 734). J. Antibiot., 1989, vol. 42, no. 1, pp. 107-115, see the abstract no. 147191m.	1-21